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ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

When Does Neoadjuvant Chemotherapy Really Avoid Radiotherapy? Clinical Predictors of Adjuvant Radiotherapy in Cervical Cancer

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ABSTRACT

Background. The aim of this study was to identify clinical variables that may predict the need for adjuvant radiotherapy after neoadjuvant chemotherapy (NACT) and radical surgery in locally advanced cervical cancer patients.

Methods. A retrospective series of cervical cancer patients with International Federation of Gynecology and Obstetrics (FIGO) stages IB2–IIB treated with NACT followed by radical surgery was analyzed. Clinical predictors of persistence of intermediate- and/or high-risk factors at final pathological analysis were investigated. Statistical analysis was performed using univariate and multivariate analysis and using a model based on artificial intelligence known as artificial neuronal network (ANN) analysis.

Results. Overall, 101 patients were available for the analyses. Fifty-two (51 %) patients were considered at high risk secondary to parametrial, resection margin and/or lymph node involvement. When disease was confined to the cervix, four (4 %) patients were considered at intermediate risk. At univariate analysis, FIGO grade 3, stage IIB disease at diagnosis and the presence of enlarged nodes before NACT predicted the presence of intermediate- and/or high-risk factors at final pathological analysis. At multivariate analysis, only FIGO grade 3 and tumor diameter maintained statistical significance. The specificity of ANN models in evaluating predictive variables was slightly superior to conventional multivariable models.

Conclusions. FIGO grade, stage, tumor diameter, and histology are associated with persistence of pathological intermediate- and/or high-risk factors after NACT and radical surgery. This information is useful in counseling patients at the time of treatment planning with regard to the probability of being subjected to pelvic radiotherapy after completion of the initially planned treatment.

Cervical cancer represents one of the most frequent malignancies among women worldwide.[1] Management of locally advanced cervical cancer (LACC) requires combined treatments, with the two most commonly adopted strategies being chemoradiotherapy and neoadjuvant chemotherapy (NACT) followed by radical surgery. NACT followed by surgery offers the advantage of possibly avoiding radiotherapy which is associated with multiple long-term side effects, including diarrhea, nausea, emesis, a negative impact in emotional functioning, vaginal stenosis, and decreased sexual activity.[2]

Several studies have shown response rates ranging from 73 to 88 % after NACT.[3–9] Unfortunately, a significant number of patients will still present with lymph nodal metastases, positive parametria, and large or deeply invasive cervical tumor. Although guidelines for adjuvant treatment after NACT and radical surgery are lacking, in common clinical practice adjuvant pelvic radiation is delivered when pathologic risk factors are identified. Patients are then subjected to a triple therapeutic strategy that increases overall duration of the treatment, costs, and side effects. Although combined definitive chemoradiotherapy has not been proven to be better than NACT, the

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need to deliver adjuvant radiotherapy after radical surgery is often perceived as a failure. The aim of this study was to identify clinical factors that may predict, at the time of treatment planning, which patients will most likely present with pathologic risk factors for which adjuvant radiotherapy is commonly prescribed.

MATERIALS AND METHODS

A retrospective analysis of all LACC patients treated with NACT followed by radical surgery at the National Cancer Institute (NCI) Milan from January 2007 until December 2011 was performed. Demographic, clinical, and pathologic data were retrieved from a prospectively collected electronic database. Missing data were integrated with surgical reports and clinical charts. The study was approved by the Institutional Review Board.

Patients with histologically confirmed squamous cell carcinoma, adenosquamous carcinoma, and adenocarcinoma of the cervix, and International Federation of Gynecology and Obstetrics (FIGO) stage IB2–IIB subjected to platinum-based NACT followed by type B or C radical hysterectomy and bilateral pelvic lymphadenectomy with or without bilateral salpingo-oophorectomy were eligible for the study.[10–12] Pretreatment evaluation included medical history collection, physical examination, magnetic resonance imaging (MRI) of the pelvis, and either computed tomography (CT) scan of the thorax and abdomen or positron emission tomography (PET); CT scan was performed on every patient based on the physician's preference. Lymph nodes measuring greater than 1 cm in diameter at MRI or CT scan, or with an increased standard uptake value at PET–CT scan, were considered positive for metastatic disease.

All patients were treated with a cisplatinum weekly dose intensity of at least 25 mg/m^2 for a period of 6–12 weeks. Drugs used in combination with cisplatinum included paclitaxel, ifosfamide, topotecan, and adriamycin.[3,13,14] Surgery was planned at 3 weeks from the last cycle of chemotherapy. Response to NACT was evaluated based on response evaluation criteria in solid tumors (RECIST) criteria, clinical examination, MRI, CT scan, or PET–CT scan.[15] The decision to deliver adjuvant radiotherapy was based on tumor board multidisciplinary discussion.

Since guidelines for adjuvant treatment in this setting are lacking, two algorithms based on different pathological risk factors were developed for statistical analysis. The first algorithm included patients with evidence of high-risk factors defined as lymph nodal metastases, parametrial involvement, and/or positive resection margin. The second algorithm included patients with high- and intermediate-risk factors. Intermediate-risk factors are defined as a combination of tumor size, depth of stromal invasion, and lymphovascular invasion (LVSI) in the absence of extracervical disease. These risk factors currently indicate the need for adjuvant chemoradiotherapy and radiotherapy in patients who have undergone surgery for early-stage disease, and are commonly adopted in the NACT setting.[16–20]

Demographic and clinical-pathologic characteristics were evaluated using the basic descriptive statistics. Via univariate analysis, variables predicting intermediate- and/or high-risk factors at final pathological analysis were evaluated based on logistic regression. Multivariate models were fit using stepwise and backward variable selection methods considering all variables with a p value <0.20 based on univariate analysis. Associations were summarized using odds ratios (ORs) and corresponding 95 % confidence intervals (CIs). Univariate and multivariate models were used to estimate the probability of receiving adjuvant treatments after surgery.

We also estimated this risk using a model based on artificial intelligence. This model, known as artificial neuronal network (ANN) analysis, was used to weight the importance of associated variables, thus predicting the effect of each variable on multifactorial phenomena. This analysis is a system of interconnections based on a simple mathematical model associated with learning algorithms. ANN mimics the function of neurons, acquiring knowledge through a learning process. It consists of a four-layer (one input layer, two hidden layers, and one output layer) feed-forward analysis. To develop the ANN, cases were randomly assigned to either the training group (80 %) or testing group (20 %) through a generator of random numbers. The back propagation of the error was applied as a learning rule using the online training method. Synaptic weights were updated after each training data record. A detailed description of ANN has been reported elsewhere.[21,22] Predicted probability from the classical multivariate model and ANN was used for the construction of receiver operating characteristic (ROC) curves. Area under the curve (AUC) estimated using the ROC analysis was used to compare the specificity of the multivariate model and ANN models in predicting the probability of a patient undergoing adjuvant treatments.

Statistical analyses were performed using the GraphPad Prism version 6.0 for Mac (GraphPad Software, San Diego, CA, USA) and IBM-Microsoft SPSS version 22.0 for Mac (IBM Corporation, Armonk, NY, USA). All p-values were two-sided, and p-values <0.05 were considered statistically significant.

RESULTS

During the study period, 104 patients with LACC were treated with NACT followed by radical surgery. Two

patients had neuroendocrine cervical carcinoma and one had clear-cell carcinoma and were therefore excluded from the study. Baseline characteristics of the patients are listed in Table 1. Mean age was 47 years. Thirty (29 %), 13 (13 %), and 58 (57 %) patients were diagnosed with FIGO stage IB2, IIA, and IIB, respectively. Eighty six (84 %), 14 (14 %), and 2 (2 %) patients had squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma, respectively.

All patients completed the planned chemotherapy and had surgery 3 weeks (range 2–5) after the completion of NACT. Complete and partial response were achieved in 27 (26 %) and 60 (60 %) patients, respectively. Fourteen patients (14 %) had stable disease. Surgery included type C1 and type B radical hysterectomy in 99 (98 %) and two (2 %) patients, respectively. Type B radical hysterectomy was performed in two cases because of extranodal disease.

Thirty-seven (37 %) patients were considered at high risk secondary to parametrial, resection margin, and/or lymph node involvement at final pathological analysis. Seventeen (17 %), 1 (1 %), and 32 (32 %) patients had parametrial, resection margin, and lymph node involvement, respectively. Eleven (11 %) patients had both parametrial and lymph node involvement; one (1 %) patient had positive margins, positive parametria, and lymph node involvement. When tumor was confined to the cervix, eight (8 %) patients were considered at intermediate risk.

For algorithm 1, at univariate analysis, FIGO grade 3 (OR 2.97; 95 % CI 1.12–7.85; $p = 0.02$), stage IIB at diagnosis (OR 3.52; 95 % CI 1.43–8.65; $p = 0.006$), and presence of enlarged nodes detected at work-up prior to NACT (OR 1.98; 95 % CI 0.86–4.59; $p = 0.10$) predicted the need for adjuvant radiotherapy. At multivariate analysis, only stage IIB at diagnosis (OR 2.90; 95 % CI 1.14–7.50; $p = 0.002$) maintained statistical significance. A trend towards the presence of a high-risk factor was observed for patients with FIGO grade 3 tumor (OR 2.49; 95 % CI 0.89–6.71; $p = 0.08$).

For algorithm 2, at univariate analysis, FIGO grade 3 (OR 3.12; 95 % CI 1.25–7.78; $p = 0.01$), stage IIB at diagnosis (OR 2.37; 95 % CI 1.04–5.40; $p = 0.03$), and large tumor diameter (OR 1.27 per 1-cm increase in diameter; 95 % CI 0.90–1.79; $p = 0.16$) predicted the need for adjuvant radiotherapy. At multivariate analysis, only FIGO grade 3 (OR 3.07; 95 % CI 1.15–8.19; $p = 0.02$) maintained statistical significance. Table 2 displays the results of univariate and multivariate analyses for both algorithms.

Using the ANN model, FIGO grade 3 (importance 0.208) and stage IIB at diagnosis (importance 0.197) were the most important variables for algorithm 1. The model estimated the importance of tumor diameter in 0.148 per

TABLE 1 Patient characteristics

Characteristic	*N*/mean (25–75 centiles)
Number of patients	101
Age (years)	47 (39–58)
BMI (kg/m^2)	24 (21–27)
Histology (%)	
Squamous cell carcinoma	86
Adenocarcinoma	13
Adenosquamous	2
Grading	
G1	3
G2	30
G3	63
NA	5
FIGO stage	
IB2	30
IIA	13
IIB	58
Positive lymph nodes on CT/PET-CT scan	38
Negative lymph nodes on CT/PET-CT scan	61
NA lymph nodes on CT/PET–CT scan	2
Maximum tumor diameter (mm)	50 (40–50)
Neoadjuvant chemotherapeutic regimen	
TOPOCIS (10)	63
TIP (3)	24
TAP (11)	13
TP (3)	1
Type of surgery	
NSRH	99
Piver 2	2
PLND	101
PALND	
Sampling	4
Systematic	14
BSO	82
OR time (min)	260 (240–300)
EBL (ml)	300 (200–600)
Number of PRBC transfusions	1 (0–2)
Clinical response	
CR	27
PR	60
SD	14
PD	0
Pathologic characteristics	
Maximum tumor diameter (mm)	10 (2–16)
LVSI	
NA	4
Positive	62
Negative	35

TABLE 1 continued

Characteristic	*N*/mean (25–75 centiles)
Deep stromal invasion	44
Positive parametria	17
Positive lymph nodes	32
Vaginal involvement	34
Adjuvant treatment	
None	47
Chemoradiotherapy	25
Radiotherapy	24
Chemotherapy	5

1-cm increase. Similarly, FIGO grade 3 (importance 0.250), tumor diameter (importance 0.213), and stage IIB at diagnosis (importance 0.181) were the most important variables for algorithm 2.

The specificity of ANN models in evaluating predictive variables was slightly superior to conventional multivariable models. In particular, evaluating the first algorithm AUC was more accurate than the multivariable model. AUC for the ANN model was 0.69 (standard error 0.58; $p = 0.004$), while AUC for the multivariable model was 0.53 (standard error 0.68; $p = 0.57$). No between-model differences were observed, evaluating algorithm 2. AUC for the ANN model was 0.68 (standard error 0.59; $p = 0.006$), while AUC for the multivariable model was 0.69 (standard error 0.60; $p = 0.003$) for algorithm 2. Figures 1 and 2 show ANN and ROC analyses.

The probability of a patient having pathologic risk factors for which adjuvant radiotherapy is usually delivered, in accordance with the two algorithms, is displayed in Table 3. Of note, a patient affected by a stage IB2, FIGO grade 1 or 2 cervical carcinoma without enlarged nodes detected at preoperative work-up before NACT had a 7 and 14 % probability of receiving adjuvant therapy when considering algorithms 1 and 2, respectively. On the contrary, a patient affected by stage IIB and enlarged nodes detected at work-up prior to NACT had an approximately 60 % probability of receiving adjuvant therapy using algorithms 1 and 2, respectively.

DISCUSSION

In our series, approximately half of the patients underwent adjuvant pelvic radiotherapy. These data fit within a very wide range reported in the literature.[3,23] Currently, we recommend adjuvant pelvic chemoradiation, in the presence of both high- and/or intermediate-risk factors.[20] Similarly, since the publication of Gynecologic Oncology Group (GOG) 92, Eddy et al. reported radiotherapy protocol violations for pathological risk factors to the cervix, despite the lack of extrauterine disease, in a prospective randomized GOG protocol on NACT followed by radical surgery in stage IB2 cervical cancer patients.[23]

Multiple series have investigated prognostic factors in LACC patients subjected to NACT followed by radical surgery; however, this is the first study reporting on variables that may precociously identify patients who will need adjuvant radiotherapy at the end of the planned treatment. We have considered two scenarios. In the first, radiotherapy is delivered only to patients with evidence of high-risk factors (algorithm 1), and in the second case, radiotherapy is delivered to patients with high- and/or intermediate-risk

TABLE 2 Univariate and multivariate analysis for high- and intermediate- plus high-risk factors

Characteristics	High-risk (algorithm 1)		Intermediate- and high-risk (algorithm 2)	
	Univariate (95 % CI)	Multivariate (95 % CI)	Univariate (95 % CI)	Multivariate (95 % CI)
Age (OR per 10-unit increase)	0.85 (0.61–1.20); $p = 0.37$		0.84 (0.60–1.17); $p = 0.31$	
BMI (OR per 5-unit increase)	1.01 (0.62–1.61); $p = 0.99$		0.94 (0.59–1.50); $p = 0.81$	
Non-squamous histology	0.47 (0.61–1.85); $p = 0.28$		0.51 (0.14–1.78); $p = 0.29$	
FIGO Grade 3	2.97 (1.12–7.85); $p = 0.02$	2.49 (0.89–6.71); $p = 0.008$	3.12 (1.25–7.78); $p = 0.01$	3.07 (1.15–8.19); $p = 0.02$
FIGO Stage IB2 vs. II IB2 and IIA vs. IIB	1.89 (0.74–4.48); $p = 0.18$ 3.52 (1.43–8.65); $p = 0.006$	2.90 (1.14–7.50); $p = 0.02$	1.58 (0.66–3.81); $p = 0.30$ 2.37 (1.04–5.40); $p = 0.03$	1.75 (0.71–4.37); $p = 0.23$
Tumor diameter (OR per 1-cm increase)	1.22 (0.86–1.74); $p = 0.24$		1.27 (0.90–1.79); $p = 0.16$	1.32 (0.89–1.94); $p = 0.16$
Enlarged nodes at preoperative workup	1.98 (0.86–4.59); $p = 0.10$	1.40 (0.55–3.54); $p = 0.46$)	1.60 (0.70–3.61); $p = 0.25$	

BMI body mass index, *FIGO* International Federation of Gynecology and Obstetrics, *OR* odds ratio

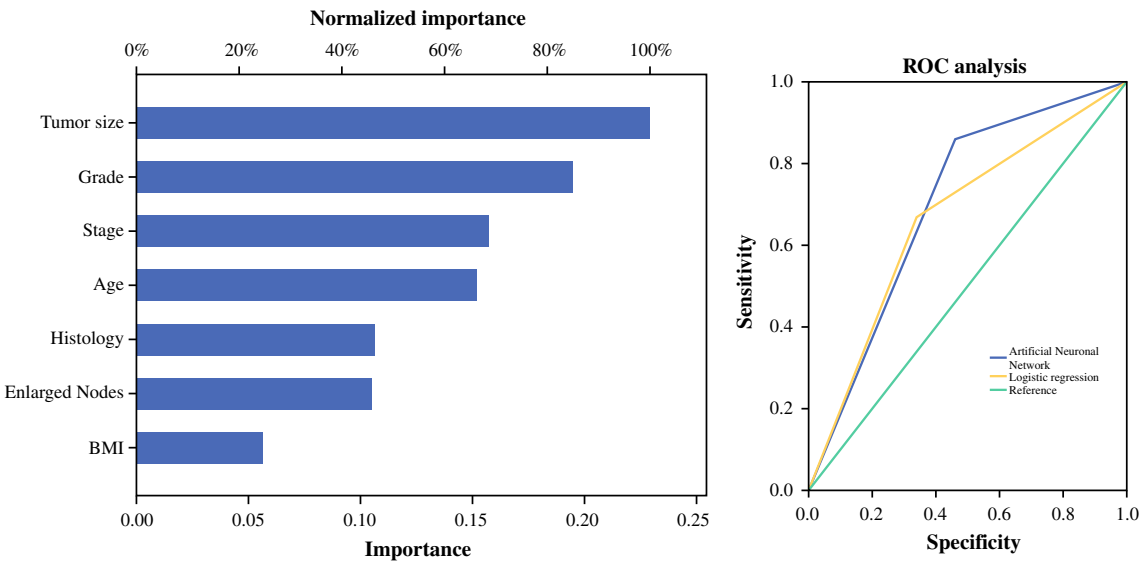

FIG. 1 ANN analysis of the importance of independent variables for predictors of high-risk pathologic factors and ROC curves between ANN analysis and logistic regression. *ANN* artificial neuronal network, *ROC* receiver operating characteristic, *BMI* body mass index

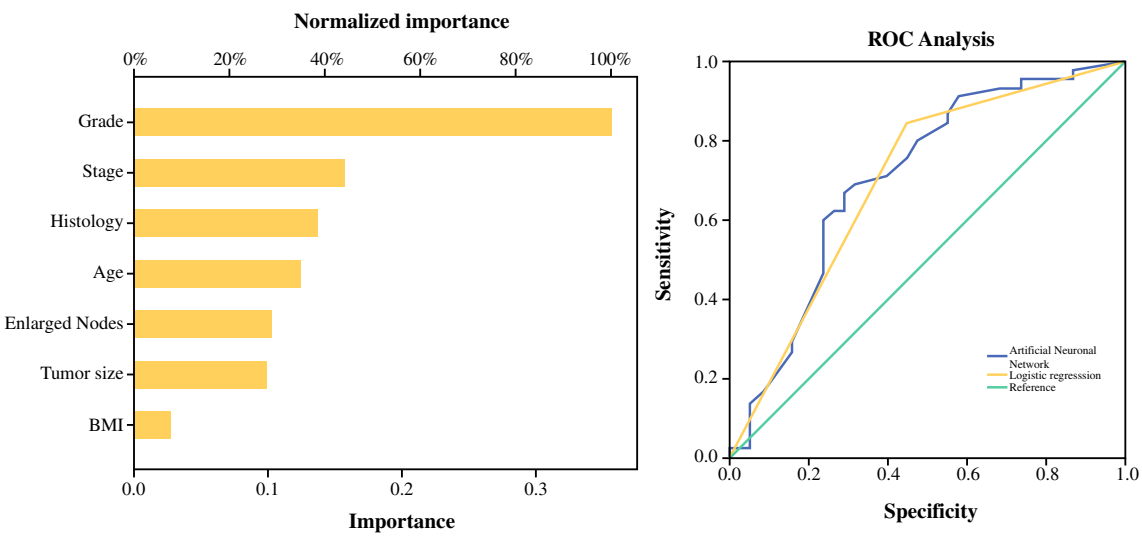

FIG. 2 ANN analysis of the importance of independent variables for predictors of intermediate- and/or high-risk pathologic factors and ROC curves between ANN analysis and logistic regression. *ANN* artificial neuronal network, *ROC* receiver operating characteristic, *BMI* body mass index

factors (algorithm 2). In algorithm 1, stage IIB disease at the time of diagnosis was the only clinical variable associated with an increased risk of the need for adjuvant radiotherapy at multivariate analysis. FIGO Grade 3 approached, but did not reach, statistical significance. In algorithm 2, FIGO grade 3 was the only clinical variable associated with an increased risk of the need for adjuvant radiotherapy at multivariate analysis. Using an ANN model tumor diameter, stage IIB disease at diagnosis and FIGO grade 3 were predictive variables for both algorithms.

Although tumor grade is usually not considered pivotal in cervical cancer, it correlated, along with parametrial involvement, with disease-free interval in GOG 49.[16] In a prospective, randomized trial comparing chemoradiotherapy with radiotherapy followed by hysterectomy, in patients with bulky stage I cervical cancer tumor grade and size were significant prognostic factors at Cox regression analysis.[24] Interestingly, in a retrospective study of 128 patients with LACC subjected to NACT followed by radical surgery, poor tumor grade affected response to

TABLE 3 Probability of a patient having pathologic risk factors for which adjuvant radiotherapy is usually delivered, in accordance with algorithms 1 and 2

	Algorithm 1 (high risk) (%)	Algorithm 2 (intermediate and/or high risk) (%)
Stage IB2–IIA, FIGO Grade 1 and 2, negative nodes at preoperative radiologic work-up	7	14
Stage IB2–IIA, FIGO Grade 1 and 2, positive nodes at preoperative radiologic work-up	0	25
Stage IIB, FIGO Grade 1 and 2, negative nodes at preoperative radiologic work-up	27	27
Stage IB2–IIA, FIGO Grade3, negative nodes at preoperative radiologic work-up	36	57
Stage IB2–IIA, FIGO Grade 3 positive nodes at preoperative radiologic work-up	38	38
Stage IIB, FIGO Grade 3, negative nodes at preoperative radiologic work-up	50	60
Stage IIB, FIGO Grade 3, positive nodes at preoperative radiologic work-up	53	58
Stage IIB, FIGO Grade 1 and 2, positive nodes at preoperative radiologic work-up	100	100
Stage IIB, any FIGO grade, positive nodes at preoperative radiologic work-up	59	64

FIGO International Federation of Gynecology and Obstetrics

chemotherapy, with an OR of 2.2 without, however, reaching statistical significance.[25] The same study identified stage III disease, bilateral parametrial involvement, non-squamous histology, and tumor size greater than 5 cm as clinical variables significantly affecting response to chemotherapy.

Both tumor size and stage express disease extension and have previously been identified as variables affecting outcome.[25] Larger tumors have larger areas of hypoxia, with an increasing amount of cells in the resting phase that are less responsive to chemotherapy.

Given the results of a randomized trial comparing NACT followed by surgery to definitive radiotherapy, NACT is currently indicated in stage IB2–IIB patients.[26] This may further change once results from the European Organisation for Research and Treatment of Cancer (EORTC) 55994 ongoing randomized trial are available.

In GOG 49, tumor size was identified as one of the most important prognostic predictors of outcome of 545 node-negative patients with disease clinically confined to the uterus.[16] Similarly, Stehman et al. reported tumor size as one of the negative prognostic factors at multivariate analysis of 626 LACC patients pooled from three GOG trials and treated with radiation therapy and various other agents.[27] More recently, tumor size was identified as the most important prognostic factor in patients with bulky stage IB cervical cancer randomized to radiation therapy with and without extrafascial hysterectomy and in patients undergoing chemoradiotherapy.[24,28]

In the last decades, the use of statistical tools in medicine has evolved dramatically, thus allowing the evaluation of the effects of multifactorial phenomena. Widespread use of the multivariate model in medical research improved the value of investigations. Similarly, ANN analysis is a computer-based model that may be useful in evaluating the effects of different covariates. Here, we tested both of these two sophisticated statistical methods (multivariate and ANN model) in order to predict the probability of cervical cancer patients treated with NACT to undergo adjuvant therapy. Despite the inherent difference between the two models, we observed similar results in terms of accuracy between systems, thus confirming the efficacy of these tools.

Weaknesses of the study include its retrospective nature and the use of different NACT regimens. However, given the cisplatin dose intensity of the different regimens used, it is very unlikely that this may have led to a bias. The fact that data were retrieved from a prospectively collected electronic database, as well as the short time-span of the study, represent strengths of this study.

Although a recent GOG randomized trial failed to prove any advantage of NACT in stage IB2 cervical cancer patients, this approach is a popular treatment strategy in many countries. In the GOG trial, pathologic prognostic factors, survival, and percentage of patients addressed to adjuvant radiotherapy were similar between the two treatment groups.[23] These data are in contrast with data from multiple trials that have demonstrated an increase in operability and in regression of the cervical and metastatic lesions. Several factors may justify this apparent discrepancy; however, the major difference between the schedule administered by Eddy et al. and most other trials is the overall platinum dose delivered. Most authors adopt courses of three cycles of chemotherapy, with a platinum dose ranging from 75 to 100 mg/m^2 compared with 50 mg/m^2, as used in GOG 141.[3,5,13,14,23,29] As a result, the total platinum dose ranges between 225 and 300 mg/m^2 before surgery compared with 150 mg/m^2. With these doses, the reported complete pathological response rate ranges

between 15 and 25 %, significantly higher than the 5 % reported in GOG 141.

CONCLUSIONS

FIGO grade 3, non-squamous histology, stage IIB disease, and large tumor diameter as assessed at diagnosis are associated with the persistence of pathological intermediate- and/or high-risk factors after NACT and radical surgery. This information is useful in providing thorough counseling based on clinical variables that can be easily assessed at the time of treatment planning with regard to the probability of being subjected to pelvic radiotherapy after completion of the treatment plan.

DISCLOSURE Andrea Papadia, Filippo Bellati, Giorgio Bogani, Antonino Ditto, Fabio Martinelli, Domenica Lorusso, Cristina Donfrancesco, Maria Luisa Gasparri, Francesco Raspagliesi declare no conflicts of interest.

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